Ethnic minority under-representation in clinical trials

Whose responsibility is it anyway?

Mahvash Hussain-Gambles
Centre for Research in Primary Care, University of Leeds, Leeds, UK

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Abstract *Ethnic minority people are frequently under-represented in clinical trials. This potentially affects the generalisability/external validity of the trial findings. This not only has important repercussions regarding the safety and the efficacy of new drug use in ethnic minority groups, but also reduces opportunities for subgroup analysis. There can be no scientific basis for excluding this group of people from clinical trials. Aims to provide a mix of theoretical and empirical debates, in order to make sense of ethnic minority exclusion from clinical trials, and suggest possibility of change. Recommends that educational programmes should be directed at clinical trial investigators and funding bodies, to increase their awareness of under-representation of ethnic minority people in clinical trials. Ethics committees could also redress this inequality by providing guidance for investigators, and by being more rigorous about reviewing clinical trial protocols. Provides a set of guidelines to "enlighten" and aid health professionals in working with ethnic, linguistic and culturally diverse populations. The guidelines require additional work and have cost implications. Argues that cost should not be allowed as an acceptable excuse for excluding ethnic minority people from clinical trials.*

Ethnic minority people are frequently under-represented in clinical trials (Heiat *et al.*, 2002), and recent findings suggest that this is happening in the UK (Mason *et al.*, 2002). There is little empirical evidence to explain their relative absence, nor the effect this may have on trial results, which could be based on unrepresentative populations. Few peer-reviewed articles clearly stipulate exclusion criteria or, especially in the UK, the study populations' ethnic background. A UK-based review of randomised controlled trials (RCTs) of statins over the last decade showed that only eight out of 47 RCTs were specific about ethnicity and these were all US-based (Bartlett *et al.*, 2003). Consequently the paucity of ethnic minority recruitment data and the absence of inclusion/exclusion criteria in the published literature makes it difficult to assess accurately the relative presence or absence of this group among clinical trial study participants (Hall, 1999).

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Addressing this is important, since gender differences in drug metabolism (Magee *et al.*, 2001), and in the anatomical location and extent of disease for certain solid tumours (McCann, 2000) are well documented. Response to drugs, metabolisms of drugs, concurrent diseases and counter-indications have also been shown to vary considerably between different ethnic groups (Krecic-Shepard *et al.*, 2000). More recently, scientists have identified gene variations responsible for the higher risk of congestive heart failure among African Americans (Gottlieb, 2002). There are also variations within different ethnic groups, and in terms of health status, South Asian people differ not only from the majority population, but also from each other (Nazroo, 1997). Differences in drug metabolism, are therefore attributed to complex interactions between genetic factors and the environment. Yet there is still a surprising lack of scientific information on ethnic differences in drug response, particularly since it is imperative that medical professionals fully disclose drug action in various populations.

Since clinical trials provide the dataset, which informs the judicious use of new drugs, exclusion of a subset of the population from clinical trials means that important information on the proper use of drugs in that subset is not available. This has important repercussions regarding the safety and the efficacy of new drug use in ethnic minority groups. The exclusion of ethnic minority people from clinical trials, not only challenges the external validity (generalisability) of trial findings, by limiting their widespread applicability, but also precludes opportunities for meaningful sub-group analyses, which determines if ethnic origin influences how the intervention works.

Apart from poor science, exclusion from clinical trials further raises issues around equity in health care provision since there is some evidence to suggest that people who take part in clinical trials are better off than those who do not. A review by Edwards *et al.* (1998), shows that on average, properly conducted clinical trials tend to benefit the participants (Edwards *et al.*, 1998). Studies also show that patients in clinical trials, even in the control arms, tend to have better outcomes than patients not enrolled in trials (Karjalainen and Palva, 1989; Davis *et al.*, 1985). There is limited evidence to suggest better psychological outcomes for trial participants, than non-participants (Edwards *et al.*, 1998), and that patients who enrol in clinical trials, do so because it gives them hope (Kahn *et al.*, 1998). Exclusion of ethnic minority people from clinical trials, also denies patients "state-of-the-art" treatment for diseases, frequent follow-up consultations and closer disease monitoring and management (Heiat *et al.*, 2002). There can, therefore, be no scientific basis for excluding this group of people from clinical trials, and exclusion therefore, suggests a form of institutional racism in which minority ethnic populations are denied the same opportunities as the general population. Exclusion of ethnic minority people also undermine the Governments' NHS plan of tacking inequalities and its core principle of providing culturally appropriate and accessible care for different groups and individuals (Department of Health, 2000).

The USA has made attempts to address this inequality through the introduction of the National Institute of Health's (NIH) mandatory guidelines, the NIH Revitalisation Act of 1993, which requires all NIH-supported research projects to include women and ethnic minority groups in all human subject research and in phase III clinical trials, so that valid analyses of differences in intervention effect can be accomplished. Since the introduction of the NIH Revitalisation Act, research investigators have been increasingly struggling to understand and to implement these guidelines (Hohmann and Parron, 1996). More generally, the guidelines on a blanket inclusion of women and minorities in clinical trials has opened up a Pandora's Box of discussions around the ambiguities surrounding the definition and the use of ethnicity as a variable (Swanson and Ward, 1995). Legislation mandating the inclusion of ethnic minority people in clinical trials may also be seen as undermining an individual's right not to participate in medical research, and the guidelines may encourage some researchers to include ethnic minority people as a token gesture in order to secure funding from the NIH.

Generally, running and recruiting into clinical trials is a costly business. Addition of "extra variables" such as women and ethnic minority people, to perform subgroup analysis, means that substantially more people have to be recruited into the trial in order to get the same effect or power. Since the inclusion of women and ethnic minority people in clinical trials affects the power of the study, it invariably affects its cost, as illustrated by an analysis of different enrolment mixes in a well-known American study, the Multiple Risk Factor Intervention Trial (MRFIT). Meinert (1999) showed that the cost of running MRFIT would have increased from 115 million to 1.846 billion dollars for gender and race mix.

Active inclusion of ethnic minority people in clinical trials has substantial resource implications, since a large number of persons eligible for the study are required to permit selecting subgroups in representational proportions. Also, investigators need to identify the characteristics of potential participants before inviting them into the study, thus putting additional demands on the already depleted resources. Representative sampling, and in particular the inclusion of ethnic minority populations, therefore, occurs against a background of more general organisational and practical difficulties.

Inclusion of ethnic minority people should be determined by the scientific question under examination and its relevance to such groups. It is not suggested that every study should include all ethnic minority groups. Exclusion of ethnic minority groups from clinical trials should only be allowed if there is substantial scientific evidence to suggest that there is no significant difference between the effects that the trial variables have on these groups. Unless these population groups are routinely included in clinical trials, this information is not available. Inclusion of ethnic minorities is, for this reason, essential in accurately assessing the applicability of research findings to

subgroups of the population. Scientific publications should also be encouraged to include results of subset analyses, even if the analysis reveals no subset differences, a statement to that effect, indicating the subset analysed could be of value. Exclusion of any groups should be based on science, and not the convenience of the investigator.

There is a need for multi-centre research ethics committees (MRECs) to look for evidence that the investigators are satisfactorily addressing the inclusion policy in the proposal. Such evidence may include information on the population characteristics of the disease or condition under study. National and local demographics of the population, along with knowledge and understanding of the ethnic/cultural characteristics of the population will also enable the development of culturally sensitive research methods, materials and data collection instruments such as questionnaires. These need to be incorporated in the design and implementation of research projects to ensure that issues such as language, education, health beliefs and customs and access to healthcare are appropriately addressed. This knowledge will inform the design of culturally sensitive studies, enable appropriate enrolment of ethnic minority people and ensure that the benefits of the research are made available to all ethnic minority communities.

MRECs have acknowledged that there may be potential problems in obtaining informed consent for patients for whom English is not the first language and they prefer "special arrangements" to be made (no guidance is available to investigators on how to achieve this). This allows some trials to exclude ethnic minority people on the basis of inability to understand the consent process. When challenged on the lack of clear guidance on this issue, the Central Office for Research Ethics Committees (COREC) advised that any "special issues" around ethnic minority recruitment, for example the inability to understand English, should be discussed with the administrator of the research ethics committee applied to, to get a steer before submitting an application.

On a more pragmatic level, there is a need to establish favourable logistical factors, such as staffing, structure and organisation of randomised clinical trials in order to identify trial designs which are attractive not only to patients, but also to the clinicians. There is a need for funding bodies to consider seriously the increased cost implications of outreach efforts to improve ethnic minority participation in research. Reimbursement for expenses or costs of bilingual staff/translators should be included, and justified as part of the necessary components of the research. Economic considerations should not, however, be used as an excuse for the exclusion of ethnic minority people from clinical trials. Good science is expensive, and since the distribution of resources depends on priorities, it is a question of how high up the priority list is the problem of unequal representation in clinical trials.

To conclude, there is a need for educational programmes aimed at investigators, ethics committees and funding bodies to increase awareness of

under-representation of ethnic minority people in clinical trials. Ethics committees could also redress this inequality by providing guidance for investigators and by being more rigorous about reviewing clinical trial protocols. A set of guidelines have been developed (see below) to "enlighten" and to provide guidance in working with ethnic, linguistic, and culturally diverse populations. The guidelines may require additional work and have cost implications. Unless this is recognised by the scientific community, there is a real danger that ethnic minority people will continue to be unequally represented in clinical trials.

The following are the proposed guidelines that may be useful in the initial planning phase of a study:

- Obtain information on the population characteristics of the disease or condition under study, and local demographics of the population.
- Identify the proportion of each ethnic minority population group to include in the study sample and the denominator used to determine this proportion.
- Where possible, culturally sensitive research methods, materials, and data collection instruments should be used in the design and implementation of research projects.
- Study participants should be provided with a choice of either translated information sheets or interpreters for the informed consent process.
- Community involvement and commitment from relevant community groups and organisations should be sought for the planned study.
- Quality control procedures should be employed in the translation of questionnaires, such as translation from English to the other language and then back to English, to ensure that the information is conveyed correctly.
- Justification should be made in support of additional staffing needs for outreach/community plans.
- The funding bodies should make allowances for the costs of outreach efforts to improve ethnic minority participation in research, such as reimbursement for travelling expenses or bilingual staff/translators.

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